REMARKS

Claims 20, 22, 25-39, 41, and 44-50 are currently pending in the application, and all stand rejected. The above amendment and the following remarks are submitted in response to the Office Action mailed July 13, 2004. Reconsideration is respectfully requested.

Claim Objection

In response to the objection to Claim 3, this claim was previously canceled and it is submitted that the objection should be withdrawn as moot. Applicants also note that Claim 25 has been amended to avoid confusion.

Obviousness Type Double Patenting

In response to the Examiner's rejection of Claims 20, 22, 25-38, 41, and 44-50 under the judicially created doctrine of obviousness-type double patenting as being based on U.S. Patent Nos. 5,820,583, 6,056,715, 6,210,394, 6,413,961, 6,254,585, 6,420,432, 6,492,332 and 6,645,168, and the provisional rejection of Claims 20, 22, 25-39, 41, and 44-50 under the judicially created doctrine of obviousness-type double patenting based on U.S. Patent Application No. 10/180,815, Applicants submit herewith a Terminal Disclaimer in accordance with 37 C.F.R. § 1.321(c) to overcome the rejection.

Rejection under 35 USC §112, First Paragraph

All pending claims stand rejected under 35 USC §112, first paragraph, for a lack of enablement based on the claiming of a solution including at least one tumor necrosis factor (TNF) soluble receptor for use in inhibiting "pain and inflammation." The Examiner notes that, while one of the activities of TNF is to produce inflammation, there is no disclosure in the instant application or in the prior art that TNF produces pain. In response, Applicants cite herewith copies of various abstracts published prior to November 5, 1998 (the priority date for the TNF soluble receptor disclosure in the instant application) indicating a role of the pro-inflammatory

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cytokine TNF in the pathogenic mechanisms of neuropathic pain (Hori, Sommer (*Exp.Neurol*), Chou, Sommer (*Pain*)), including the enhancement of nociception at peripheral inflammatory tissues, and activity of agents that block TNF in attenuating pain and inflammation (Sander, Fenner, Breedveld, Qiang, Camussi). Pathologic mechanisms of pain and inflammation are often linked, as recognized by the present inventors. One of ordinary skill in the art at the time of application filing would recognize the role of TNF in pain, as evidenced by the abstracts cited concurrently herewith. Applicants submit that the enablement rejection should be withdrawn.

Rejection under 35 USC §112, Second Paragraph

Claims 29 and 44 are rejected under 35 USC §112, second paragraph, for being indefinite due to use of the term "metabolic transformation." As noted by the Examiner, while the term is not explicitly defined, the term is used multiple times in the specification. In addition, the Examiner's attention is directed to the specification at page 8, line 31, through page 9, line 4, in which advantages of local administration are discussed including "(3) local administration of the active agents directly to a wound or operative site also substantially reduces degradation of the agents through extracellular processes, e.g., first- and second-pass metabolism, that would otherwise occur if the agents were given orally, intravenously, subcutaneously or intramuscularly." Applicants also enclose herewith an excerpt from *Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition*, pp. 11-12 (1996), for a discussion of metabolic transformation, i.e., "the biotransformation of drugs and other xenobiotics into more hydrophilic metabolites...." It is submitted that one of ordinary skill will understand, based on the specification and in view of the teachings in standard texts, that metabolic transformation is the conversion of one chemical entity to another and may occur in the liver and/or other tissue including the kidneys, gastrointestinal tract, skin, lungs, and/or plasma such as through first- or first- and second-pass metabolism.

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Priority Determination

Applicants respectfully direct the Examiner's attention to U.S. Provisional Patent Application No. 60/107,256 filed November 5, 1998 and International Patent Application No. PCT/US99/26330 filed November 5, 1999, and designating the United States, from which applications priority has been previously claimed under 35 USC §§ 119 and 120, respectively. The instant claims are fully supported in these two priority applications, including disclosure of soluble TNF receptors (sTNFR) and rhTNFR:Fc, and Applicants respectfully submit all pending claims are entitled to a priority date of November 5, 1998. Applicants acknowledge that the priority chain for other aspects of the disclosure and claims is complex, and regret any inconvenience.

Rejection under 35 USC § 102 Based on Smith et al.

Solution Claims 39 and 41 stand rejected under 35 USC § 102 based on the disclosure of U.S. Patent No. 5,945,397 to Smith et al. The Examiner notes that Smith et al. teach solutions comprising soluble TNF receptors, wherein the solutions comprise carriers, and pharmaceutical compositions and methods of therapeutic treatment. However, Applicants submit that Smith et al. clearly envision only systemically administered compositions, as evidenced by the disclosure at Column 16, lines 12-13: "Appropriate *dosages* can be determined in trials." Dosages (e.g., mg of drug/kg of body weight) are indicative of systemically administered compositions, rather than locally administered compositions. This is reinforced by the disclosed indications, cachexia and septic shock (Column 16, lines 24-25), system wide disorders that must be treated systemically rather than locally.

In contrast, Claim 39 is directed to a solution for use in the preemptive inhibition of pain and inflammation at a wound during a surgical procedure, comprising at least one sTNFR in a "liquid irrigation carrier," reflecting local irrigation rather than systemic injection or other

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systemic administration. Additionally, Claim 39 as amended is directed to solutions including the sTNFR "at a concentration that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically." Thus the instant claims are clearly directed to solutions that are at low concentration and in a liquid irrigation carrier as is suitable for local perioperative irrigation rather than systemic administration and treatment. These aspects of the invention are neither disclosed nor suggested by Smith et al.

Applicants also teach that the claimed locally delivered compositions avoid side effects associated with systemically administered drugs (see, e.g., page 3, lines 3-6, page 8, lines 25-27). While the sTNFR disclosed in Smith et al. has proven very successful, it has been associated with a potential serious side effect in some patients with chronic or recurrent infections, pre-existing infections, diabetes, or other conditions that predispose them to infection. See the enclosed FDA Talk Paper, "New Warning for Arthritis Drug, Enbrel" (May 12, 1999). Applicants submit that such systemic side effects are believed to be avoided by the presently claimed locally delivered compositions.

For all of the above reasons, Applicants submit the rejection based on Smith et al. should be withdrawn.

Rejection under 35 USC § 102 Based on Lai

Solution Claims 39, 41, and 44-50 stand rejected under 35 USC § 102 based on the disclosure of U.S. Patent No. 5,747,532 to Lai. Lai discloses pharmaceutical compositions comprising soluble TNF receptors and IL-1 receptor antagonists. Lai discloses the delivery of such compositions "orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like." Column 7, lines 52-53. Suitable dosages are disclosed as ranging from 1 ug per

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kg of body weight to 100 mg per kg of body weight. All disclosure is clearly directed to compositions delivered for systemic uptake and effect rather than local delivery to the site of a surgical procedure.

For all of the same reasons submitted above with respect to Smith et al., which is also limited to systemic treatments rather than local procedural delivery, Applicants submit that Claim 39 and claims dependent therefrom define patentable subject matter over Lai. Claims 49 and 50 (as amended) are similar to Claim 39, calling for solutions deliverable during a surgical procedure in a "liquid carrier for perioperative application" (Claim 49) or a "liquid carrier" (Claim 50), and including at least one sTNFR at a concentration that is sufficient to provide a level of inhibitory effect at the wound when delivered locally to the wound and that results in a plasma concentration that is less than a plasma concentration that would be required to achieve the same level of inhibitory effect at the wound when delivered systemically. Applicants thus submit that this rejection also should be withdrawn.

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Conclusion

Applicants submit that each of Claims 20, 22, 25-39, 41, and 44-50 are in condition for allowance. Reconsideration and passage of the application to issue is respectfully requested. Should the Examiner have any questions, she is invited to call the undersigned attorney.

Respectfully submitted,

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Enclosures:

Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, Ninth Edition, pp. 11-12 (1997)
FDA Talk Paper, "New Warning for Arthritis Drug, Enbrel" (May 12, 1999)

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: 1/13/05 Carole Julyan

DKS:cj

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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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Fat as a Reservoir. Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in starvation it constitutes 10% of body weight; hence, fat can serve as an important reservoir for lipid-soluble drugs. For example, as much as 70% of the highly lipid-soluble barbiturate thiopental may be present in body fat 3 hours after administration. However, fat is a rather stable reservoir because it has a relatively low blood flow.

Bone. The tetracycline antibiotics (and other divalent-metal-ion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone-crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium into the blood; their effects can thus persist long after exposure has ceased. Local destruction of the bone medulla also may lead to reduced blood flow and prolongation of the reservoir effect, since the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results whereby the greater the exposure to the toxic agent the slower is its rate of elimination.

Transcellular Reservoirs. Drugs also cross epithelial cells and may accumulate in the transcellular fluids. The major transcellular reservoir is the gastrointestinal tract. Weak bases are passively concentrated in the stomach from the blood, because of the large pH differential between the two fluids, and some drugs are secreted in the bile in an active form or as a conjugate that can be hydrolyzed in the intestine. In these cases, and when an orally administered drug is slowly absorbed, the gastrointestinal tract serves as a drug reservoir.

Other transcellular fluids, including cerebrospinal fluid, aqueous humor, endolymph, and joint fluids, do not generally accumulate significant total amounts of drugs.

Redistribution. Termination of drug effect usually is by biotransformation and excretion, but it may also result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or by inhalation. The factors involved in redistribution of drugs have been discussed above.

Placental Transfer of Drugs. The potential transfer of drugs across the placenta is important, since drugs may cause congenital anomalies. Administered immediately before delivery, they also may have adverse effects on the neonate. Drugs cross the placenta primarily by simple diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Penetration is least with drugs possessing a high degree of dissociation or low lipid solubility. The view that the placenta is a barrier to drugs is inaccurate. A more appropriate approximation is that the fetus is to at least some extent exposed to essentially all drugs taken by the mother.

BIOTRANSFORMATION OF DRUGS

The lipophilic characteristics of drugs that promote their passage through biological membranes and subsequent access to their site of action hinder their elimination from the body. Renal excretion of unchanged drug plays only a modest role in the overall elimination of most therapeutic agents, since lipophilic compounds filtered through the glomerulus are largely reabsorbed through the tubular membranes. The biotransformation of drugs and other xenobiotics into more hydrophilic metabolites is therefore essential for the termination of their biological activity, and the elimination of these compounds from the body. In general, biotransformation reactions generate more polar, inactive metabolites that are readily excreted from the body. However, in some cases, metabolites with potent biological activity or toxic properties are generated. Many of the metabolic biotransformation reactions leading to inactive metabolites of drugs generate biologically active metabolites of endogenous compounds. The following discussion focuses on the biotransformation of drugs, but is generally applicable to the metabolism of all xenobiotics as well as a number of endogenous compounds, including steroids, vitamins, and fatty acids.

Phase I and Phase II Biotransformations. Drug biotransformation reactions are classified as either phase I functionalization reactions or phase II biosynthetic reactions. Phase I reactions introduce or expose a functional group on the parent compound. Phase I reactions generally result in the loss of pharmacological activity, although there are examples of retention or enhancement of activity. In rare instances, metabolism has been associated with an altered pharmacological activity. Prodrugs are pharmacologically inactive compounds, designed to maximize the amount of the active species that reaches its site of action. Inactive prodrugs are converted rapidly to biologically active metabolites, often by the hydrolysis of an ester or amide linkage. If not rapidly excreted into the urine, the products of phase I biotransformation reactions can then react with endogenous compounds to form a highly water soluble conjugate.

Phase II conjugation reactions lead to the formation of a covalent linkage between a functional group on the parent compound with glucuronic acid, sulfate, glutathione, amino acids, or acetate. These highly polar conjugates are generally inactive and are excreted rapidly in the urine and feces. An example of an active conjugate is the glucuronide metabolite of morphine, which is a more potent analgesic than its parent compound. High molecular weight conju-

gates excreted in the bile are subject to enzymatic cleavage of the conjugate bond by intestinal microflora and release of the parent drug back into the systemic circulation. This phenomenon of enterohepatic recirculation may be associated with a delayed elimination of drug from the body and a prolongation of effect.

Site of Biotransformation. The metabolic conversion of drugs generally is enzymatic in nature. The enzyme systems involved in the biotransformation of drugs are localized in the liver, although every tissue examined has some metabolic activity. Other organs with significant metabolic capacity include the kidneys, gastrointestinal tract, skin, and lungs. Following nonparenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the liver or intestines before it reaches the systemic circulation. This first-pass metabolism significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drug-metabolizing activity is found in the endoplasmic reticulum and the cytosol, although drug biotransformations also can occur in the mitochondria, nuclear envelope, and plasma membrane. Upon homogenization and differential centrifugation of tissues, the endoplasmic reticulum breaks up, and fragments of the membrane form microvesicles, referred to as microsomes. The drug-metabolizing enzymes in the endoplasmic reticulum therefore often are classified as microsomal enzymes. The enzyme systems involved in phase I reactions are located primarily in the endoplasmic reticulum, while the phase II conjugation enzyme systems are mainly cytosolic. Often drugs biotransformed through a phase I reaction in the endoplasmic reticulum are conjugated in the cytosolic fraction of the same cell.

Cytochrome P450 Monooxygenase System. The cytochrome P450 enzyme family is the major catalyst of drug biotransformation reactions. Since its origin more than 3.5 billion years ago, the cytochrome P450 gene family has diversified to accommodate the metabolism of a growing number of environmental chemicals, food toxins, and drugs. The resulting superfamily of enzymes catalyzes a wide variety of oxidative and reductive reactions and has activity towards a chemically diverse group of substrates. Cytochrome P450 enzymes are heme-containing membrane proteins localized in the smooth endoplasmic reticulum of numerous tissues. These hemoproteins are in close association with a second membrane protein, NADPH–cytochrome P450 reductase, in a ratio of about ten cytochrome P450 molecules per one reductase. The flavoprotein reductase contains equimolar amounts of flavin mononucleotide and flavin adenine dinucleotide and is the source of one or both of the electrons required for the oxidation reaction. The interaction between the cytochrome P450 and reductase proteins is facilitated by the lipid bilayer in which they are embedded.

Oxidative reactions catalyzed by the microsomal monooxygenase system require the cytochrome P450 hemoprotein, NADPH–cytochrome P450 reductase, NADPH, and molecular oxygen. The multiple-step oxidation reaction is depicted schematically in Figure 1–3. The xenobiotic substrate reacts with the oxidized (Fe^{3+}) form of cytochrome P450 to form an enzyme–substrate complex. The cytochrome P450 reductase accepts an electron from NADPH, which in turn reduces the oxidized cytochrome P450–xenobiotic complex. The reduced (Fe^{2+}) cytochrome P450–substrate complex then reacts with molecular oxygen and a second electron from NADPH donated through the same flavoprotein reductase to form an activated oxygen species. In the final steps, one atom of oxygen is released as H_2O and the second atom of oxygen is transferred to the substrate. Upon release of the oxidized substrate, the oxidized cytochrome P450 enzyme is regenerated. Oxidative biotransformations catalyzed by cytochrome P450 monooxygenases include aromatic and side chain hydroxylation, N-, O-, and S-dealkylation, N-oxidation, sulfoxidation, N-hydroxylation, deamination, dehalogenation, and desulfuration. A number of reductive reactions also are catalyzed by cytochrome P450 enzymes, generally under conditions of low oxygen tension. The only common structural feature of the diverse group of xenobiotics oxidized by cytochrome P450 enzymes is their high lipid solubility. Details and examples of cytochrome P450–catalyzed biotransformations are shown in Table 1–2.

Twelve cytochrome P450 gene families have been identified in human beings, and a number of distinct cytochrome P450 enzymes often exist within a single cell. A standard classification system for the cytochrome P450 multigene family is based on the sequence similarity of the individual proteins. Members of a given gene family have >40% amino acid identity. A given cytochrome P450 family is further divided into subfamilies, such that protein sequences within the same subfamily are >55% identical. The cytochrome P450 1, 2,

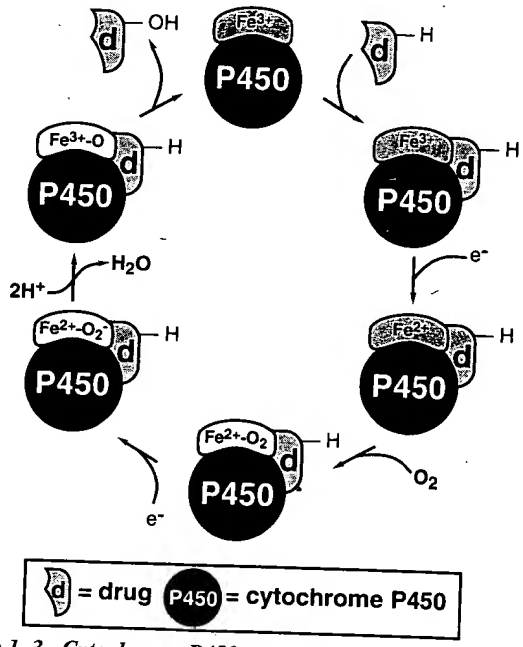

Figure 1–3. Cytochrome P450 mechanism of oxygen activation and drug oxidation.

The heme iron at the active site is shown as Fe. The electrons are supplied from NADPH via cytochrome P450 reductase.

FDA
TALK PAPER

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NEW WARNING FOR ARTHRITIS DRUG, ENBREL

FDA is advising physicians about new safety concerns regarding the use of etanercept (Enbrel), a product recently approved to treat moderate to severe rheumatoid arthritis (RA). New postmarketing reports indicate that certain patients receiving Enbrel have developed serious infections, including sepsis, and that several of these patients have died from their infections.

The Immunex Corporation, Seattle, Wash., the co-sponsor of Enbrel, (along with Wyeth-Ayerst Laboratories, Philadelphia, Pa.) is sending a "Dear Doctor" letter alerting physicians to the new safety concerns, reminding them of the current label warning and informing them that the labeling for Enbrel has been revised to incorporate the new information.

Enbrel was approved last November with labeling that says that it should not be given to patients with sepsis and should be discontinued if a patient develops a serious infection.

Because of new information obtained from adverse reaction reports to FDA and Immunex, the warning related to sepsis has been expanded to include patients with any active infection, including chronic or localized infections.

In addition, it is now recommended that patients who develop a new infection while being treated with Enbrel be monitored closely.

It is further recommended that physicians be cautious when considering prescribing Enbrel to patients with a history of recurring infections or with underlying conditions such as advanced or poorly controlled diabetes that may predispose them to infections.

Since the drug's approval, 30 of the estimated 25,000 patients treated with Enbrel are reported to have developed serious infections, including sepsis. Six of these patients died within two to sixteen weeks after starting treatment. A number of these RA patients had a history of chronic or recurrent infections, pre-existing infections, diabetes, or other conditions that predisposed them to infections.

Even though many RA patients are predisposed to infections, significant concerns remain that Enbrel may contribute to the occurrence of serious infections. Many of the infections occurred shortly after initiation of Enbrel therapy. In addition, a controlled study of Enbrel to treat sepsis showed a higher incidence of death in patients treated with Enbrel. Moreover, Enbrel inhibits the action of tumor necrosis factor, a component of the body's natural defenses against serious infection.

To date, controlled clinical studies have not shown an increase in serious infections in patients receiving Enbrel. FDA has requested that Immunex perform additional studies to assess the risk of serious infection related to Enbrel therapy.

At this time, without further controlled clinical studies, it is unclear whether Enbrel truly is the cause of the serious infections in patients with RA. However, as a precautionary measure, physicians should consider these new reports when assessing the risks and benefits of Enbrel.

Enbrel, a genetically engineered protein, was approved to treat patients with symptoms of moderate to severe, active RA who have not responded well to other treatments. It can significantly reduce pain and swollen joints in people disabled with RA, an autoimmune disease that affects more than two million Americans.

FDA requests that all cases of serious infection or sepsis occurring in patients taking Enbrel be reported to the agency through MEDWATCH. Reports to Medwatch should be made by phone to 1-800-FDA-1088, by fax to 1-800-FDA-0178, by mail to MEDWATCH, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857. Reports can also be made through the internet at www.fda.gov/medwatch/. Health professionals may also contact Wyeth-Ayerst Product Information at 1-800-934-5556 or Immunex Professional Services at 1-800-IMMUNEX (1-800-466-8639).

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